BEYER WEAVER & THOMAS, LLP
INTELLECTUAL PROPERTY LAW
500 12th Street, Suite 200, Oakland, CA 94607
Telephone: (510) 663-1100 Facsimile: (510) 663-0920
www.beyerlaw.com

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August 31, 2006

Receiver: **Examiner Tran, My Chau T.**
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Denise S. Bergin

Serial No. 09/874,091
Our Ref. No.: 1680.002/CHIRP014

Re: Appeal Brief

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Fax Contents: Fax Cover Sheet- 1 page
Appeal Brief Transmittal (2 copies)- 4 pages
Appeal Brief-33 pages

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: Charych, et al.

Application No.: 09/874,091

Filed: June 4, 2001

Title: MICROARRAYS FOR PERFORMING PROTEOMIC ANALYSES

Attorney Docket No.: 1680.002/CHIRP014

Examiner: Tran, My Chau T.

Group: 1639

CERTIFICATE OF FACSIMILE TRANSMISSION
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Signed: Natalie Morgan
Natalie Morgan

APPEAL BRIEF TRANSMITTAL
(37 CFR 192)

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P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

This brief is in furtherance of the Notice of Appeal filed in this case on April 24, 2006.

This application is on behalf of

☐ Small Entity ☒ Large Entity

Pursuant to 37 CFR 1.17(f), the fee for filing the Appeal Brief is:
☐ $250.00 (Small Entity) ☒ $500.00 (Large Entity)

☒ Applicant(s) hereby petition for a two-month extension(s) of time to under 37 CFR 1.136.

If an additional extension of time is required, please consider this a petition therefor.

☐ An extension for months has already been secured and the fee paid therefor of $ is deducted from the total fee due for the total months of extension now requested.

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☒ Applicant(s) believe that no (additional) Extension of Time is required; however, if it is determined that such an extension is required, Applicant(s) hereby petition that such an extension be granted and authorize the Commissioner to charge the required fees for an Extension of Time under 37 CFR 1.136 to Deposit Account No. 500388.

Total Fee Due:

Appeal Brief fee	$500
Extension Fee (if any)	$450
Total Fee Due	$950

☐ Enclosed is Check No. in the amount of $.

☒ Please charge the required fees and credit any overpayment to Deposit Account No. 500388, (Order No. CHIRP014). Two copies of this transmittal are enclosed.

Respectfully submitted,
BEYER WEAVER & THOMAS, LLP

Denise Bergin

Denise S. Bergin
Reg. No. 50,581

P.O. Box 70250
Oakland, CA 94612-0250
(510) 663-1100

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PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

EX PARTE Charych *et al.*

Application for Patent

Filed: June 4, 2001

Serial No. 09/874,091

FOR:

MICROARRAYS FOR PERFORMING PROTEOMIC ANALYSES

APPEAL BRIEF

CERTIFICATE OF FACSIMILE TRANSMISSION
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Signed: Natalie Morgan

Natalie Morgan

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(1) REAL PARTY IN INTEREST

Novartis Vaccines and Diagnostics
4560 Horton Street
Emeryville, California 94608-2616

(2) RELATED APPEALS AND INTERFERENCES

N/A

(3) STATUS OF CLAIMS

There are a total of 33 claims pending in this application (claims 1, 60-73 and 79-91 and 97-101). Claims 2-59, 74-78 and 82-96 have been cancelled. Claims 1, 60-73, 79-91 and 97-101 have been examined and rejected.

Specifically, claims 1, 60, 61, 63-66, 73, 79, 80, 82-85, 97, 98 and 99-101 are rejected under 35 U.S.C. §103(a) as being unpatentable over US Patent No. 5,478,527 to Gustafson et al. ("Gustafson") in view of US Patent No. 6,087,102 to Chenchik et al. ("Chenchik").

Claims 62 and 81 are rejected under 35 U.S.C. §103(a) as being unpatentable over Gustafson and Chenchik, as applied above to claim 1 or 73, and further in view of US Patent No. 6,329,209 to Wagner et al. ("Wagner").

Claims 67-72 and 86-91 are rejected under 35 U.S.C. §103(a) as being unpatentable over Gustafson and Chenchik, as applied above to claim 1 or 73, and further in view of US Patent No. 5,482,867 to Barrett et al. ("Barrett").

The rejection of each of claims all claims under § 103 is appealed.

(4) STATUS OF AMENDMENTS

Claims 1 and 73 were amended in response to the Final Office Action mailed December 21, 2005. These amendments were entered as indicated in the Advisory Action mailed March 22, 2006.

(5) SUMMARY OF CLAIMED SUBJECT MATTER

Independent claim 1

The pending claims are directed to particular arrays of protein-binding agents stably attached to the surface of a solid support, and kits incorporating such arrays. Independent claim 1 recites the following:

> 1. An array of protein-binding agents stably attached to the surface of a solid support, said array comprising:
>
> a solid substrate having a substantially planar surface comprising a layer of aluminum formed on a glass base material, the aluminum coated with a silicon dioxide coating having a thickness of between about 200 and 900Å;
>
> a plurality of different protein-binding agents bound to said substrate, each of said protein-binding agents comprising,
>
> an anchoring segment stably bound to the substrate surface,
>
> a peptidomimetic protein-binding segment, and
>
> a linker segment connecting and separating the anchoring and peptidomimetic segments.

Claim 1 describes an array of protein-binding agents that is configured for analysis of protein binding. The array includes a solid substrate and a plurality of different protein binding agents that are attached to the substrate. The arrays described by the claim are configured for analyses of protein binding that are performed by contacting labeled protein mixtures to the array. This is discussed generally at page 7, lines 20-28.

The solid substrates have a substantially planar that may take the form of various configurations including that of a microscope slide. This concept is discussed at page 9, line 19 – page 10, line 12 and page 10, lines 27-33. The substrate is a composite of different layers of material including a glass base, (see, e.g., element 112a in Fig. 1A) and surface coating materials aluminum and silicon dioxide (see, e.g., element 112b Fig. 1A).

The aluminum is coated with a silicon dioxide coating having a thickness between about 200 and 900Å. As noted in the specification, for example, at page 21, line 13 to page 22, line 15, the present inventors have discovered that the presence of a silicon dioxide coating of this thickness on the aluminum substrate surface can amplify the fluorescent signal used to read the arrays with resultant improvement in performance of the arrays in practice. See also page 36, lines 1-4. Aluminum slides coated with silicon dioxide are also discussed on page 21, line 13 – page 22, line 14. See also page 28, line 3 to page 30, line 13.

The arrays of the invention also include "a plurality of different protein-binding agents bound to said substrate." This is significant to the context of the invention – protein microarray technology. As described on page 18, under the heading "General Features of the Array," the array is characterized by having a plurality of protein-binding agent spots on a solid substrate. The number of different chemical species of protein-binding agent present on the surface of the array is at least 2, or at least 10, or at least 100, and can be much higher, generally being at least about 1,000, or at least about 5,000 to about 50,000, for example, between about 5,000 and about 10,000 (page 18, lines 19-23). This allows high throughput protein binding assays. Figure 1B shows a plurality of different protein binding agents on the substrate surface (reference number 100). See also Figure 2, which depicts an array (206) having a plurality of different protein-binding agents stably associated with the surface of a solid support. Also, see Figures 9A-9C, which depict scans of microarray chips bearing a library of 1,000 peptoid-based protein-binding agents.

Each of the protein-binding agents comprises an anchoring segment stably bound to the substrate surface, a peptidomimetic protein-binding segment, and a linker segment connecting and separating the anchoring and peptidomimetic segments. These segments are shown in Figure 1A and discussed in the section "Protein-Binding Agents," which begins on page 14, line 27. Figure 1C shows a specific example of a protein-binding agent.

Examples of anchoring segments include activated silanes, e.g., chlorosilane or an alkoxysilane. Anchoring segments are discussed on page 11, lines 11-22. Figure 1C also shows an example of an anchoring group, biotin (104).

Peptidomimetic protein-binding segments are nonpeptide synthetic polymers or oligomers that detectably interact with proteins or receptors in a manner analogous to

protein-protein or protein-peptide physical and/or chemical interactions under assay conditions. In some cases, the peptidomimetic may also mimic the folding of natural proteins. Peptidomimetics include peptoids. Peptidomimetics are discussed on page 14, line 32 – page 15, line 28. Figure 1C shows an example of a peptidomimetic (102).

The linking segment of the protein-binding agent molecule is chosen to provide for separation between the solid surface and the peptidomimetic segment sufficient to facilitate interaction between the peptidomimetic and the components of the analyte solution. It is discussed on page 16, line – page 17, line 3 of the specification. Figure 1C shows an example of a linker (106).

Independent Claim 73

Independent claim 73 recites:

A kit for use in performing a differential binding assay, said kit comprising:

an array comprising

a solid substrate having a substantially planar surface comprising a layer of aluminum formed on a glass base material, the aluminum coated with a silicon dioxide coating configured to amplify a fluorescent signal from a labeled protein bound to the array;

a plurality of different protein-binding agents bound to said substrate, each of said protein-binding agents comprising,

an anchoring segment stably bound to the substrate surface,

a peptidomimetic protein-binding segment, and

a linker segment connecting and separating the anchoring and peptidomimetic segments; and

one or more reagents for conducting a differential binding assay.

Kits incorporating arrays and reagents for conducting differential binding assays are discussed generally on page 5, lines 12-18 and page 33, lines 31-37.

The claimed kit includes an array comprising "a solid substrate having a substantially planar surface comprising a layer of aluminum formed on a glass base material, the aluminum coated with a silicon dioxide coating configured to amplify a fluorescent signal from a labeled protein bound to the array." Amplification of fluorescent signals from labeled proteins is discussed on pages 14, lines 12-21, page 22, lines 5-13 and page 36, lines 1-4. In particular, in certain embodiments, silicon dioxide coating layer thicknesses of about 200 Å to about 900 Å are used to amplify a fluorescent signal.

Other claimed features of the substrate are discussed above with respect to claim 1. The claimed kits also include a plurality of different protein binding agents. This is discussed above with respect to claim 1.

Finally, the kits include "one or more reagents for conducting a differential binding assay." Differential binding assays are discussed generally in the section titled "3. Methods of Using the Protein-Binding Agent Arrays of the Subject Invention" that begins on page 27, line 25. Reagents for labeling proteins to be assayed are discussed in the section titled "A. Protein Labeling" on page 28, line 5. Examples of reagents include Cy3 and Cy5.

Dependent claims 97-101

Each of claims 99-101 depends directly or indirectly from claim 1 and each of claims 97 and 98 depend from claim 73.

Claim 99 depends from claim 1 and specifies that array also contains a "plurality of fluorescently labeled proteins, comprising at least two proteins labeled with different fluorescent labels, bound to one or more of the protein-binding agents." As discussed in the specification, a plurality of fluorescently labeled proteins having different fluorescent labels may be used in differential binding assays. Differential binding assays are discussed on page 28, lines 11-14, and in reference to Figure 5 on page 29, line 33 – page 30, line 14.

Claim 100 depends from claim 99 and specifies that the fluorescent labels are amine reactive dyes. Claim 101 depends from claim 100 and specifies that the fluorescent labels are Cyanine 3 and Cyanine 5. This is discussed on page 28, line 25 – page 29, line 4 and on page 36, lines 1-4. As discussed at page 36, the recited silicon dioxide thickness allows amplification of the Cy3 and Cy5 signals.

Claim 97 depends from claim 73 and specifies that the fluorescent labels are amine reactive dyes. Claim 98 depends from claim 97 and specifies that the fluorescent labels are Cyanine 3 and Cyanine 5. This is discussed on page 28, line 25 – page 29, line 4 and on page 36, lines 1-4. As discussed at page 36, the recited silicon dioxide thickness allows amplification of the Cy3 and Cy5 signals.

(6) GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

Claims 1, 60-73 and 79-91 and 97-101 are pending in the application.

Claims 1, 60, 61, 63-66, 73, 79, 80, 82-85, 97, 98 and 99-101 stand rejected under 35 U.S.C. §103(a) as being unpatentable over US Patent No. 5,478,527 to Gustafson et al. ("Gustafson") in view of US Patent No. 6,087,102 to Chenchik et al. ("Chenchik").

Claims 62 and 82 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Gustafson and Chenchik, as applied to claim 1, and further in view of US Patent No. 6,329,209 to Wagner et al. ("Wagner").

Claims 67-72 and 86-91 are rejected under 35 U.S.C. §103(a) as being unpatentable over Gustafson and Chenchik, as applied to claim 1, and further in view of US Patent No. 5,482,867 to Barrett et al. ("Barrett").

(7) ARGUMENTS

Rejection of claims 1, 60, 61, 63-66, 73, 79, 80, 82-85, 97, 98 and 99-101 under U.S.C. § 103(a) as being unpatentable over Gustafson in view of Chenchik

Introduction And Summary

Claims 1, 60, 61, 63-66, 73, 79, 80, 82-85, 97, 98 and 99-101 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Gustafson in view of Chenchik. The patentability of claims 1, 73 and 97-101 will be argued separately. The Appellants' explanation of the differences between the above-cited references and the claimed invention will first be discussed for independent claim 1, then for dependent claims 99-101. The Appellants explanation of the differences between the references and the

claimed invention will then be discussed for independent claim 1 and claims 97 and 98, which depend from claim 73.

The pending claims are directed to particular arrays of protein-binding agents stably attached to the surface of a solid support, and kits incorporating such arrays. Importantly, the claims require a plurality of different protein-binding agents stably attached to the surface. As discussed above, this limitation is important to the context of the invention – microarrays for high throughput binding assays.

The arrays and kits are used for conducting proteomic analyses such as differential binding assays in which the binding of a particular protein that has been labeled with a fluorescent dye to an array element is detected by a fluorescence-based detection system. The pending claims are directed to arrays having a plurality of different protein-binding agents that are configured for optimal effectiveness of the fluorescence-based detection. Specifically, the claims have previously been focused on a particular embodiment of the invention wherein aluminum on a glass substrate surface is coated with a particular configuration of silicon dioxide on the aluminum substrate surface. As described above, the claimed embodiment is designed to optimize the effectiveness of a fluorescence-based detection system.

The primary reference, Gustafson, is directed to a fundamentally different type of substrate and assay technology, specifically, reflective diffraction biogratings. The biograting of Gustafson is specific to its diffraction technique, which is capable of analyzing only a single analyte. Moreover, while the arrays of the invention are configured to optimize the effectiveness of a fluorescent-based detection system of fluorescently labeled probes, Gustafson does not involve labeled proteins.

Chenchik is directed to arrays of multiple polymeric targets used to assay labeled probes. Among other distinctions from the claimed invention, Chenchik does not disclose a solid substrate comprising a layer of aluminum formed on a glass base material, the aluminum coated with a silicon dioxide coating having a thickness of between about 200 and 900Å.

The Examiner's rejection attempts to graft aspects of the arrays of multiple polymeric targets used in the labeled assays in Chenchik onto the diffraction gratings of Gustafson. Appellants submit that Gustafson relates to such fundamentally different arrays and assay techniques than both Chenchik and the claimed invention that one of

skill would not arrive at the claimed invention from the combination of Gustafson and Chenchik.

Gustafson's teaching of the use of a flat substrate of silicon dioxide on reflective metal would have been viewed as specific to their particular label-free assay. One of skill in the art would not have viewed Gustafson as relevant to assays involving labeled proteins. Moreover, the diffraction grating of Gustafson is premised on using a single type of protein-binding agent. There is no teaching or suggestion of how to incorporate multiple protein-binding agents into a workable diffraction grating. Even if one were to modify Gustafson in the manner the Examiner suggests, i.e., by adding multiple protein-binding agents, it would render the diffraction grating as taught in Gustafson inoperable.

Fundamentally the concepts of an array of multiple different protein-binding agents and signal amplification of labeled probes are lacking in Gustafson. As the primary reference, Gustafson requires more modification than can be supplied by Chenchik. Gustafson does not come close to the claimed invention.

Independent Claim 1

As discussed above, claim 1 recites an array of protein-binding agents stably attached to the surface of a solid support, comprising

"a solid substrate...comprising a layer of aluminum formed on a glass base material, the aluminum coated with a silicon dioxide coating having a thickness of between about 200 and 900Å,"

and

"a plurality of different protein-binding agents bound to said substrate"

Appellants submit that Gustafson in combination with Chenchik does not render claim 1 unpatentable under 35 U.S.C. § 103(a) for at least the following reasons for at least the following reasons:

A) There is no teaching or suggestion of how to modify Gustafson in the manner the Examiner suggests.

B) Because the Examiner's proposed modification would render Gustafson unsuitable for its intended purpose, a proper suggestion or motivation to combine the references has not been asserted.

C) At least because Gustafson does not relate to labeled assays, one of skill in the art would not have been motivated to combine the references.

The Cited References

As indicated above, the independent claims are rejected over Gustafson in view of Chenchik. Gustafson and Chenchik describe very different products to be used in very different assays. The primary reference, Gustafson, is specifically addressed to providing a suitable substrate for its reflective diffraction biograting. Chenchik, by contrast, relates to arrays of multiple polymeric targets used to assay labeled probes.

The diffraction biogratings of Gustafson are formed by parallel linear zones of a single active and deactivated binding reagent. The zones form a diffraction grating when the active reagent binds with its opposite member of its binding pair. (col. 1, lines 25-35 and 44-49). In various embodiments, Gustafson describes substrates composed of silicon applied over silicon dioxide (e.g., see Fig. 4) and in which silicon dioxide is applied over a reflective metal deposited on silicon. The objective is to provide an optically flat reflective substrate that apparently enhances reflective diffraction from a biograting formed on the substrate.

As described in Gustafson, diffraction gratings work by causing incident light to be diffracted into specific angles as opposed to being scattered in all directions. The diffraction biogratings of Gustafson are formed by parallel linear zones of a single active and deactivated binding reagent. The zones form a diffraction grating when the active reagent binds with its opposite member of its binding pair. (col. 1, lines 25-35 and 44-49).

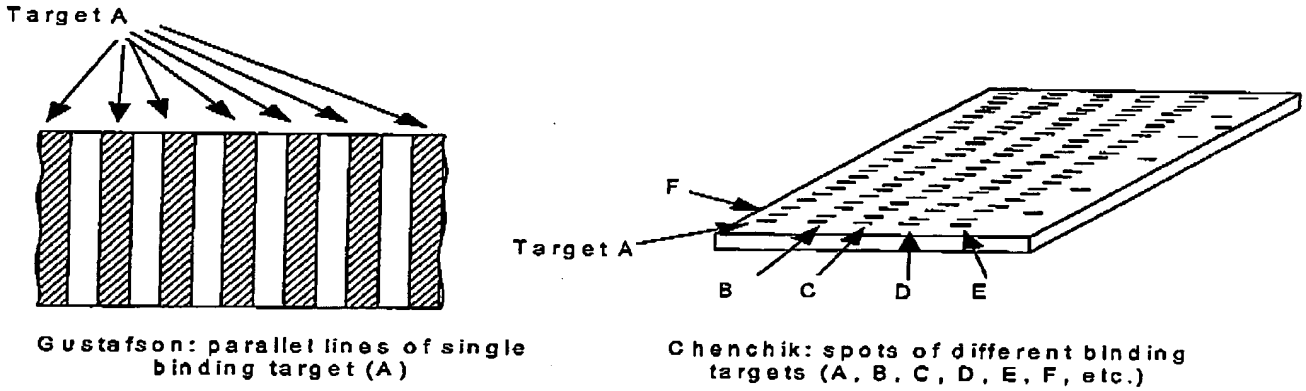
Thus, the Gustafson assays work by contacting the diffraction grating with a sample analyte, illuminating the surface and measuring the light detected at the light diffraction angles. If the analyte binds to the active reagent, a diffraction grating is formed. Light detected at the diffraction angles correlates to the quantity of the analyte (col. 1, lines 63-67). Thus, it is the arrangement of the reagent molecules in parallel linear zones, and not labeled analytes, that allows the detection of the presence and

quantity of an analyte. Nowhere does Gustafson teach or suggest that its diffraction grating may be used to detect more than one analyte, nor how one would use a diffraction pattern to do so.

To fully appreciate the differences between the products of the cited references, Appellants have annotated the following schematics:

1) Appellants' rendering of a top view of the diffraction biograting taught in Gustafson based on Gustafson Fig. 1, and

2) Fig. 1 from Chenchik, which shows a top view of the biochip array:



Gustafson: parallel lines of single binding target (A)

Chenchik: spots of different binding targets (A, B, C, D, E, F, etc.)

On the left, a top view of the biograting shown in Fig. 1 of Gustafson is shown. As can be seen from the schematic, a single binding agent ("target A" in the schematic) forms parallel linear zones of active and inactive target A. When contacted with a solution having the binding partner of target A, the binding partners bind to form a diffraction grating. It is necessary that target A forms parallel linear zones so that when contacted with an analyte solution containing the opposite member of its binding pair, the bound pairs form a diffraction grating. The binding partner of target A is detected by the resulting diffraction pattern – if target A did not form parallel linear zones, the binding of target A and the partner would not form a diffraction grating. Thus, the entire context of Gustafson is premised on a single target bound on a substrate densely enough to form parallel lines that will diffract incident light when bound to its analyte partner.

Chenchik, by contrast, describes arrays of polymeric targets that can bind a plurality of proteins. The arrays are made up of patches of polymeric targets in discrete,

known regions on a substrate (targets A, B, C, D, E, F, etc. in the schematic). Each position in the array represents a unique size (col. 5, lines 35-40). The assays work by contacting the arrays with a sample solution and detecting the presence or absence of a labeled probe bound to each target (col. 5, lines 35-40). The density of the array is low enough to provide adequate resolution of binding events with a probe carrying a variety of different labels (col. 5, lines 9-14). Chenchik discusses a wide variety of detection methods depending on the particular label used, e.g., fluorescent labels (col. 10, lines 38-44). Nowhere does Chenchik teach or suggest that a diffraction grating may be formed by any arrangement of its patches, nor that diffraction patterns may be used to detect the presence of proteins in the sample solution.

Recent Prosecution

The rejections of the currently pending claims are set forth in the February 8, 2005 Advisory Action, May 3, 2005 Office Action and March 22, 2006 Advisory Actions.

With respect to (A) and (B), above, the Examiner's position is that:

> "The array of Gustafson et al. differs from the presently claimed invention by failing to include a plurality of fluorescent labeled proteins...It would have been obvious to a person of ordinary skill in the art...to include a plurality of fluorescent labeled proteins in the array of Gustafson et al. for the advantage of providing a high throughput format that provides two types of informations, which are the types of genes [*sic*] expressed and the size of the expressed products...Furthermore, one of ordinary skill in the art would have reasonably expect[ed] success in the combination of Gustafson et al. and Chenchik et al. because Chenchik et al. disclose by examples the success of including [a] plurality of fluorescent labeled probe[s] that bind[] to the target on the surface of the support." (May 3, 2005 Office Action, item 19, page 8)

Although the Examiner refers to a plurality of fluorescent labeled probes in the above paragraph, Appellants also address this as applying to the plurality of different protein-binding agents bound to the substrate, as recited in claim 1. Appellants dispute the Examiner's contentions, and submit that that there is no teaching or suggestion in either reference of how one would incorporate the plurality of binding agents or probes of Chenchik with the diffraction grating of Gustafson. This is discussed further below.

With regard to (C), whether Gustafson is relevant to labeled probe signal amplification, Appellants note that this is significant because the array recited in claim 1 has a specific configuration of silicon dioxide that optimizes fluorescent signal amplification. Specific embodiments in the dependent claims and independent claim 73 (discussed below) recite fluorescent probes. Further, the assays of Chenchik are based on labeled probes, e.g., fluorescent labeled probes. Applicants have argued that Gustafson's teaching of the use of a flat substrate of silicon dioxide on reflective metal would have been viewed as specific to their particular label-free assay, and not relevant to the assays of Chenchik.

The Examiner's position is as follows:

> "Gustafson et al. does disclose the general concept of fluorescent signal amplification. For, Gustafson et al. define the term 'diffraction grating' as grating formed in one or more immunological steps. That is the diffraction grating is formed directly by the conjugation of the non-light disturbing binding agent on the insoluble surface with a light disturbing analyte (i.e., a fluorescent signal from a labeled protein bound to an array), and the type of gratings include transmission amplitude gratings (i.e., amplifying a fluorescent signal). (col. 4, lines 41-49). Thus Gustafson et al. does disclose the general concept of fluorescent signal amplification." (February 8, 2005 Advisory Action, item 5(1), page 3)

Appellants dispute this contention, and submit that Gustafson does not disclose labeled proteins or relate to fluorescent signal amplification, as discussed further below.

Also, Appellants submitted a Declaration Under 37 CFR § 1.132 by Dr. Deborah Charych, which in pertinent part addresses how a person of skill in the art would have interpreted and viewed Gustafson. This is excerpted in the arguments below. The Examiner has stated that the expert opinion submitted by Dr. Charych is inadequate to overcome the rejections because it does not meet the requirements of MPEP 716.01(c). Appellants also dispute this contention, as addressed below, and request consideration of this portion of Dr. Charych's Declaration.

A) There is no teaching or suggestion of how to modify the diffraction gratings of Gustafson to include "a plurality of protein-binding agents"

Gustafson differs from the present invention at least by failing to include a plurality of different protein binding agents. Chenchik is used to supply the array elements of

different protein binding agents. The Examiner contends that one of skill in the art would be motivated to "include a plurality of labeled proteins for the advantage of providing a high throughput format that provides two types of informations, which are the types of [protein] and the size of the expressed products."

As noted above, the two references describe very different arrangements of targets (alternating stripes of a single binding reagent or target versus discrete patches of different targets). There is no teaching or suggestion (nor indication provided by the Examiner) of how one might incorporate the multiple targets of Chenchik into the substrate of Gustafson. For example, would the resulting product have parallel lines of a binding partners or discrete patches of different targets? Would the product result in incident light being diffracted or discrete patches of labeled probes emitting signals, or both?

There is no teaching or suggestion that the arrangement would form a diffraction grating upon contact with an analyte solution, and if so, the resulting pattern would provide useful information. Even if it were possible to form a diffraction grating using multiple different targets (and it is not clear that it is), there is no teaching or suggestion of how one would analyze the resulting presence or absence of a pattern.

The arrangement of the binding agents of Gustafson and Chenchik, each crucial to the operations of its respective assays, are very different. Because the target arrangements described in Gustafson and Chenchik are so different and because the target arrangement described in each reference is crucial to the very different assay techniques, it is far from clear that one of skill in the art reviewing these references would put them together to produce a hybrid array that is at all workable much less anywhere near the claimed invention. Grafting multiple discrete patches of different targets onto the biograting of Gustafson to produce a high throughput assay, as suggested by the Examiner, requires far more insight than is reasonably supplied by the references.

B) The Examiner's Proposed Modification Would Render Gustafson Unsuitable for Its Intended Purpose

The purpose of the substrates of Gustafson is to provide parallel zones of a binding reagent so that when contacted with a particular analyte, a diffraction grating is formed, the resulting diffraction pattern of which determines the presence and quantity of

the analyte. As discussed in the preceding section, there is no teaching or suggestion in the references, and the Examiner has not provided any explanation of how the plurality of different protein binding agents would be arranged to provide a diffraction grating.

In order to form a diffraction grating when contacted with their binding partners, the binding agents would have to form parallel linear zones; any other arrangement would not result in a diffraction pattern under any circumstance and clearly render Gustafson unsuitable for its intended purpose. However, there is no suggestion in either reference and the Examiner has not specified, how the parallel lines would be formed. Would each binding agent be in a single line, or would all binding agents mixed together so that a single line would contain multiple binding agents?

Appellants submit that all of the possible manners in which one might carry out the Examiner's proposed modification would render Gustafson unsuitable for its intended purpose. For example, if substrate contained multiple targets, each forming single line, the absence of a diffraction pattern would provide little information – the analyte solution may still contain one or more of the analytes each of which bound to its respective partner to form for example, two lines at opposite ends of the substrate. One would expect a diffraction grating to be formed only under a very narrow range of circumstances, i.e., only if most or all binding partners of the targets were present in the analyte solution and bound to their respective partners. The presence of such a diffraction pattern might provide information about the total amount of analytes present in the solution (and it is not clear that it would), but there is no indication or teaching that it would provide any information about the presence or quantity any one particular analyte.

Even if, for the sake of argument, it were possible to construct a diffraction grating using multiple binding agents some of which are bound to their respective analyte partners, it is far from clear from the combined teachings how one would analyze the resulting diffraction pattern to determine the presence and quantity of any or all of the analytes.

In short, using multiple binding regents to construct the substrate of Gustafson would result in such little information being obtainable from the presence or absence of a diffraction pattern that the proposed modification would render Gustafson unsuitable for its intended purpose.

C) At least because Gustafson does not relate to labeled assays, one of skill in the art would not have been motivated to combine the references

The preceding arguments underscore the fact that Gustafson is fundamentally different from the present claims and the Chenchik reference. The arrangement of the binding agents of Gustafson and Chenchik, each crucial to the operations of its respective assays, are very different. In addition to being premised on a single target, Gustafson does not relate to assays that employ multiple labeled probes. To find that the particular biograting substrate of Gustafson is at all relevant to the labeled assays of Chenchik (or vice versa) crosses the line into impermissible hindsight. The Examiner has contended throughout prosecution that Gustafson relates to labeled assays. Specifically, the Examiner contends the following section of Gustafson shows that the reference relates to signal amplification of a fluorescently labeled probe:

> "The term "diffraction grating", as used herein, is defined to include gratings which are formed in one or more immunological steps. For the method of this invention, the diffraction grating is formed directly by the conjugation of the non-light disturbing binding reagent on the insoluble surface with a light disturbing analyte." (col. 4, lines 41-46).

Appellants fail to see how this applies to fluorescently-labeled probes. While it may be possible to use a fluorescently-labeled analyte in the diffraction gratings of Gustafson, there would be no point in doing so. In the context of the Gustafson, a fluorescently labeled analyte is no more or less "light disturbing" than a label-free analyte; the assays work by measuring the diffraction of incident light on a diffraction grating created by the binding of the analyte. Whether sections of that diffraction grating are fluorescing (or otherwise emitting signals from labeled probes) is wholly inapposite to the operation of the assays of Gustafson.

This distinction is important because the particular claimed configuration is designed to optimize the effectiveness of a fluorescence-based detection system. A person skilled in the art would not have seen any advantage in combining the teachings of Gustafson and Chenchik since Gustafson's teaching of the use of a flat substrate of silicon dioxide on reflective metal would have been viewed as specific to its particular diffraction-based assay.

This point is underscored by the expert opinion of Dr. Deborah Charych in made of record in the Declaration Under 37 CFR § 1.132 (attached in the Evidence Appendix). The relevant section is excerpted below:

> 6. I have reviewed the references cited against the present application, in particular US Patent No. 5,478,527 to Gustafson et al. ("Gustafson"). Gustafson is directed to an entirely different type of array and assay technology that, with particular[] relevance, does even not involve labeled proteins. Rather, Gustafson is specifically addressed to providing a suitable substrate for its reflective diffraction biograting. In various embodiments, Gustafson describes substrates composed of silicon applied over silicon dioxide (e.g., see Fig. 4) and in which silicon dioxide is applied over a reflective metal deposited on silicon. The objective is to provide an optically flat reflective substrate that apparently enhances reflective diffraction from a biograting formed on the substrate. Since Gustafson's substrate is specifically designed for their biograting immunoassay, and this assay is label free (i.e., it does not make use of fluorescently labeled probes), it is my judgment that a skilled worker in this field at the time that our invention was made would not have been led to our invention by Gustafson in combination with the other cited references. I do not believe that a person skilled in the art would have seen any advantage in combining the teachings of Gustafson and the other references to which the Examiner has referred, namely Pease, Wagner and Barrett, since Gustafson's teaching of the use of a flat substrate of silicon dioxide on reflective metal would have been viewed as specific to their particular label-free assay.

Appellants submit that Dr. Charych's expert opinion regarding Gustafson meets the requirements of MPEP 716.01(c)(III) ("[O]pinion testimony...is entitled to consideration and some weight so long as the opinion is not on the ultimate legal conclusion at issue") and is entitled to consideration as relevant to how one of skill in the art would interpret and view the reference. In particular, Appellants' rely on Sections 1-4 (describing Dr. Charych's qualifications as an expert) and Section 6 (Dr. Charych's expert opinion regarding Gustafson and its relevance to the present invention).

Claim 99

Claim 99 depends from claim 1 and specifies that the array further comprises a plurality of fluorescently labeled proteins, comprising at least two proteins labeled with different fluorescent labels, bound to one or more of the protein-binding agents.

As discussed above with respect to claim 1 and below with respect to claim 73, Gustafson is not relevant to labeled proteins, or fluorescent signal amplification. The

additional claim element recited in claim 99 clearly distinguishes the claimed invention from Gustafson alone or in combination with Chenchik. For at least this reason, Applicants request withdrawal of the rejection.

Claim 100

Claim 100 depends from claim 99 and further specifies that the fluorescent labels are amine reactive dyes. As discussed above, the recited substrate configuration amplifies the fluorescent signal from such dyes. Although Chenchik discloses amine reactive dyes, Applicants submit that one of skill in the art would not combine the particular substrate described in Gustafson with this aspect of Chenchik, as the substrate of Gustafson is particular to its label-free assay. For at least this reason, Applicants request withdrawal of the rejection.

Claim 101

Claim 101 further specifies that the fluorescent labels are Cy3 and Cy5. As discussed above, the recited silicon dioxide thickness allows amplification of the signals. Although Chenchik discloses these dyes, Applicants submit that one of skill in the art would not combine the particular substrate described in Gustafson with this aspect of Chenchik, as the substrate of Gustafson is particular to its label-free assay. For at least this reason, Applicants request withdrawal of the rejection.

Independent Claim 73

Independent claim 73 recites kits for performing differential protein binding assays. The kits include an array and one or more reagents for conducting a differential binding assay.

First, the array recited in claim 73 requires a substrate having "aluminum coated with a silicon dioxide coating configured to amplify a fluorescent signal from a labeled protein bound to the array" and "a plurality of different protein-binding agents" bound to the substrate.

As with claim 1, the Examiner contends that it would be obvious to combine the silicon dioxide substrate used for a diffraction grating in Gustafson with the multiple different protein binding agents as taught in Chenchik to arrive at the claimed invention.

Appellants submit that the claim is patentable over the combination of Gustafson with Chenchik for the reasons given above with respect to claim 1.

Further, claim 73 recites that the silicon dioxide is "configured to amplify a fluorescent signal from a labeled protein bound to the array" and includes reagents for conducting a differential protein-binding assay. The arrays in accordance with the present invention are useful in performing proteomic analyses of complex protein samples. For example, in the differential binding assays, the support bound binding agents acts as targets for the analyte probes in the test sample. The analyte probe is labeled.

The Examiner has contended throughout prosecution that Gustafson relates to labeled assays. Specifically, the Examiner contends the following section of Gustafson shows that the reference relates to signal amplification of a fluorescently labeled probe. As discussed above, with respect to claim 1, there is no teaching or suggestion that Gustafson relates to labeled probes. Specifically, the Examiner contends that:

> "It is the examiner['s] position that [the] Gustafson et. al definition for the term "diffraction grating" would not only encompass the labeled free assay but would also include immunoassay step wherein the labeled analyte bind[s] with the binding pair on the surface of the support and the label produces a light signal." (March 22, 2006 Advisory Action, item 5, page 4).

Contrary to the Examiner's contention, Gustafson does not teach or suggest labeled probes or fluorescent signal amplification. As explained above, the assays work by measuring the diffraction of incident light on a diffraction grating created by the binding of the analyte. While it may be possible to use a fluorescently-labeled analyte in the diffraction gratings of Gustafson (and it is not clear that it would be) there would be no point in doing so. Whether sections of that diffraction grating are fluorescing (or otherwise emitting signals from labeled probes) is wholly inapposite to the operation of the assays of Gustafson. Rather, what is important is if and how light incident on the grating is diffracting.

Applicants also refer to the section of the Declaration above in which Dr. Charych gave her opinion as one of skill in the art, where she states that "Gustafson is directed to an entirely different type of array and assay technology that, with particular[] relevance,

does even not involve labeled proteins." The Examiner has not explained how the gratings of Gustafson would work with labeled proteins.

This distinction is important because, as explained in prior Responses, the particular claimed configuration is designed to optimize the effectiveness of a fluorescence-based detection system. A person skilled in the art would not have seen any advantage in combining the teachings of Gustafson and Chenchik since Gustafson's teaching of the use of a flat substrate of silicon dioxide on reflective metal would have been viewed as specific to its particular diffraction-based assay. There is certainly no suggestion in the references of the benefit of a substrate surface configuration that increases reflectivity of the substrate surface to enhance fluorescent signal detection as described and claimed.

Fundamentally the concepts of fluorescent signal amplification and a plurality of different protein binding agents is lacking in Gustafson. As the primary reference, Gustafson requires more modification than can be supplied by Chenchik. Gustafson does not come close to the claimed invention.

Claim 97

Claim 97 depends from claim 73 and further specifies that the fluorescent labels are amine reactive dyes. As discussed above, the recited substrate configuration amplifies the fluorescent signal from such dyes. Although Chenchik discloses amine reactive dyes, Applicants submit that one of skill in the art would not combine the particular substrate described in Gustafson with this aspect of Chenchik, as the substrate of Gustafson is particular to its label-free assay. For at least this reason, Applicants request withdrawal of the rejection.

Claim 98

Claim 98 further specifies that the fluorescent labels are Cy3 and Cy5. As discussed above, the recited silicon dioxide thickness allows amplification of the signals. Although Chenchik discloses these dyes, Applicants submit that one of skill in the art would not combine the particular substrate described in Gustafson with this aspect of Chenchik, as the substrate of Gustafson is particular to its label-free assay. For at least this reason, Applicants request withdrawal of the rejection.

Rejection of claims 62 and 81 under U.S.C. § 103(a) as being unpatentable over Gustafson in view of Chenchik and further in view of Wagner

Claim 62, which depends from claim 1, and claim 81, which depends from claim 73 have been rejected over Gustafson in view of Chenchik, as applied to claims 1 and 73 above, and further in view of Wagner.

Wagner describes arrays of protein-capture agents for the simultaneous detection of a plurality of proteins (Abstract). The arrangement of these protein-capture agents is similar to that described in Chenchik; i.e., an array of patches each of a different protein-capture agent (see col. 9, line 66 – col. 10, line 12 and Figure 1). Wagner does not remedy the deficiencies described above of the combination of Gustafson in view of Chenchik.

For at least these reasons, Applicants request withdrawal of the rejections.

Rejection of claims 67-72 and 86-91 under U.S.C. § 103(a) as being unpatentable over Gustafson in view of Chenchik and further in view of Barrett

Claims 67-72, which depends from claim 1, and claims 86-91, which depend from claim 73 have been rejected over Gustafson in view of Chenchik, as applied to claims 1 and 73 above, and further in view of Barrett.

Barrett discloses methods of immobilizing anti-ligands on surfaces of solid substrates. Barrett does not remedy the deficiencies described above of the combination of Gustafson in view of Chenchik.

For at least these reasons, Applicants request withdrawal of the rejections.

Conclusion

In view of the foregoing, it is respectfully submitted that none of the pending claims are rendered unpatentable by the cited references. Accordingly, the pending rejections of all of the claims under 35 U.S.C. § 103 should be reversed.

Respectfully submitted,
BEYER WEAVER & THOMAS, LLP

Denise Bergin

Denise Bergin
Registration No. 50,581

(8) CLAIMS APPENDIX

APPENDIX
PENDING CLAIMS

1. (previously presented) An array of protein-binding agents stably attached to the surface of a solid support, said array comprising:

a solid substrate having a substantially planar surface comprising a layer of aluminum formed on a glass base material, the aluminum coated with a silicon dioxide coating having a thickness of between about 200 and 900Å;

a plurality of different protein-binding agents bound to said substrate, each of said protein-binding agents comprising,

an anchoring segment stably bound to the substrate surface,

a peptidomimetic protein-binding segment, and

a linker segment connecting and separating the anchoring and peptidomimetic segments.

2-59. (canceled)

60. (previously presented) The array of claim 1, wherein said substrate surface further comprises an organic chemical modification group between the oxide and the protein-binding agents.

61. (previously presented) The array of claim 60, wherein said organic chemical modification group comprises an aminosilane.

62. (previously presented) The array of claim 61, wherein said aminosilane is functionalized with a maleimide.

63. (previously presented) The array of claim 62, wherein said peptidomimetic segment is a peptoid.

64. (previously presented) The array of claim 63, wherein said linker segment is selected from the group consisting of C2 – C100 aliphatic chains, polyethylene oxide, an orthogonal peptidomimetic or peptide oligomers.

65. (previously presented) The array of claim 64, wherein said anchoring segment is a thiol.

66. (previously presented) The array of claim 61, wherein said aminosilane is functionalized with an agent selected from the group consisting of hydrazide, aminooxy, N-hydroxysuccinimide, anhydride, aldehyde, disulfide, thiol, azide and phosphine.

67. (previously presented) The array of claim 61, wherein said aminosilane is functionalized with an avidin protein.

68. (previously presented) The array of claim 67, wherein said anchoring segment is biotin.

69. (previously presented) The array of claim 1, wherein said solid support comprises a silicon dioxide-coated aluminum layer on a substantially planar glass surface, the silicon dioxide being modified with a heterobifunctional maleimide-functionalized aminosilane, and wherein said plurality of different protein-binding agents bound to said substrate each comprises,

a thiol substrate anchoring segment stably bound to the maleimide-presenting substrate surface,

a peptoid protein-binding segment, and

an aliphatic linker segment connecting and separating the anchoring and peptidomimetic segments.

70. (previously presented) The array of claim 69, wherein said maleimide-functionalized aminosilane comprises succinimidyl 4-(N-maleimidomethyl)-cyclohexane-1-carboxylate.

71. (previously presented) The array of claim 1, wherein said solid support comprises a silicon dioxide-coated aluminum layer on a substantially planar

glass surface, the silicon dioxide being modified with a heterobifunctional avidin-functionalized aminosilane, and wherein said plurality of different protein-binding agents bound to said substrate each comprises,

a biotin substrate anchoring segment stably bound to the avidin-presenting substrate surface,

a peptoid protein-binding segment, and

an orthogonal peptide linker segment connecting and separating the anchoring and peptidomimetic segments.

72. (previously presented) The array of claim 71, wherein said avidin-functionalized aminosilane or aminothiol comprises an NHS-6-aminohexanoyl-6-aminohexanoyl-biotin moiety.

73. (previously presented) A kit for use in performing a differential binding assay, said kit comprising:

an array comprising

a solid substrate having a substantially planar surface comprising a layer of aluminum formed on a glass base material, the aluminum coated with a silicon dioxide coating having a thickness of between about 200 and 900Å;

a plurality of different protein-binding agents bound to said substrate, each of said protein-binding agents comprising,

an anchoring segment stably bound to the substrate surface,

a peptidomimetic protein-binding segment, and

a linker segment connecting and separating the anchoring and peptidomimetic segments;

one or more reagents for conducting a differential binding assay comprising a plurality of fluorescent labels for proteins.

74-78. (canceled)

79. (previously presented) The kit of claim 73, wherein said substrate surface further comprises an organic chemical modification group between the oxide and the protein-binding agents.

80. (previously presented) The kit of claim 79, wherein said organic chemical modification group comprises an aminosilane.

81. (previously presented) The kit of claim 80, wherein said aminosilane is functionalized with a maleimide.

82. (previously presented) The kit of claim 81, wherein said peptidomimetic segment is a peptoid.

83. (previously presented) The kit of claim 82, wherein said linker segment is selected from the group consisting of C2 – C100 aliphatic chains, polyethylene oxide, an orthogonal peptidomimetic or peptide oligomers.

84. (previously presented) The kit of claim 83, wherein said anchoring segment is a thiol.

85. (previously presented) The kit of claim 80, wherein said aminosilane is functionalized with an agent selected from the group consisting of hydrazide, aminooxy, N-hydroxysuccinimide, anhydride, aldehyde, disulfide, thiol, azide and phosphine.

86. (previously presented) The kit of claim 80, wherein said aminosilane is functionalized with an avidin protein.

87. (previously presented) The kit of claim 86, wherein said anchoring segment is biotin.

88. (previously presented) The kit of claim 73, wherein said solid support comprises a silicon dioxide-coated aluminum layer on a substantially planar

glass surface, the silicon dioxide being modified with a heterobifunctional maleimide-functionalized aminosilane, and wherein said plurality of different protein-binding agents bound to said substrate each comprises,

a thiol substrate anchoring segment stably bound to the maleimide-presenting substrate surface,

a peptoid protein-binding segment, and

an aliphatic linker segment connecting and separating the anchoring and peptidomimetic segments.

89. (previously presented) The kit of claim 88, wherein said maleimide-functionalized aminosilane comprises succinimidyl 4-(N-maleimidomethyl)-cyclohexane-1-carboxylate.

90. (previously presented) The kit of claim 73, wherein said solid support comprises a silicon dioxide-coated aluminum layer on a substantially planar glass surface, the silicon dioxide being modified with a heterobifunctional avidin-functionalized aminosilane, and wherein said plurality of different protein-binding agents bound to said substrate each comprises,

a biotin substrate anchoring segment stably bound to the avidin-presenting substrate surface,

a peptoid protein-binding segment, and

an orthogonal peptide linker segment connecting and separating the anchoring and peptidomimetic segments.

91. (previously presented) The kit of claim 90, wherein said avidin-functionalized aminosilane or aminothiol comprises an NHS-6-aminohexanoyl-6-aminohexanoyl-biotin moiety.

92-96. (canceled)

97. (previously presented) The kit of claim 73, wherein the fluorescent labels are amine reactive dyes.

98. (previously presented) The kit of claim 97, wherein the amine reactive dyes are Cyanine 3 and Cyanine 5.

99. (previously presented) The array of claim 1, further comprising a plurality of fluorescently labeled proteins, comprising at least two proteins labeled with different fluorescent labels, bound to one or more of the protein-binding agents.

100. (previously presented) The array of claim 99, wherein the fluorescent labels are amine reactive dyes.

101. (previously presented) The array of claim 100, wherein the fluorescent labels are Cyanine 3 and Cyanine 5.

(9) EVIDENCE APPENDIX

Attached is a Declaration Under 37 CFR § 1.132 by Dr. Deborah Charych, originally filed on April 6, 2005 and indicated entered by the Examiner in the May 3, 2005 Office Action.

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: Charych, et al.

Application No.: 09/874,091

Filed: June 4, 2001

Title: MICROARRAYS FOR PERFORMING PROTEOMIC ANALYSES

Attorney Docket No.: CHIRP014

Examiner: Tran, My-Chau T.

Group: 1641

DECLARATION UNDER 37 CFR § 1.132

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, Deborah Charych, declare as follows:

1. I am a co-inventor of the above-identified patent application.

2. I earned a Ph.D. in Physical / Analytical Chemistry from the University of California, Berkeley in 1992. I currently serve as Vice-Chairman of the Board of Trustees for the Gordon Research Conferences and Chairman of the Gordon Research Conference, Chemical Sensors and Interfacial Design section. I am a co-inventor on six issued U.S. patents and more than a dozen pending U.S. patent applications, and a coauthor of over 20 published papers in the fields of combinatorial chemistry, genomics and proteomics microarrays, and biomaterials.

3. I was a Principal Investigator and Program Manager in the Biomolecular Materials Program, Lawrence Berkeley National Laboratory, Berkeley, CA from 1993-1998. Since 1998, I have worked as a research scientist at Chiron Corporation, Emeryville, CA (hereinafter "Chiron"), where I currently hold the position of Senior Scientist, Proteomic and Genomic Expression Technologies/Bioorganic Chemistry.

4. My work at Chiron has focused on the development of new combinatorial synthetic methods and genomic and proteomic techniques and materials, including microarray experimental design and materials development.

5. The application presently claims an aspect of the invention directed to an array of protein-binding agents stably attached to the surface of a solid support, the array comprising a solid substrate having a substantially planar surface comprising a layer of aluminum formed on a glass base material, the aluminum coated with a silicon dioxide coating having a thickness of between about 200 and 900Å. The claimed range of silicon dioxide thickness is a critical feature of the invention presently claimed since we have found that this thickness provided optimal amplification of a fluorescent signal from a labeled protein bound to the array.

6. I have reviewed the references cited against the present application, in particular US Patent No. 5,478,527 to Gustafson et al. ("Gustafson"). Gustafson is directed to an entirely different type of array and assay technology that, with particularly relevance, does even not involve labeled proteins. Rather, Gustafson is specifically addressed to providing a suitable substrate for its reflective diffraction biograting. In various embodiments, Gustafson describes substrates composed of silicon applied over silicon dioxide (e.g., see Fig. 4) and in which silicon dioxide is applied over a reflective metal deposited on silicon. The objective is to provide an optically flat reflective substrate that apparently enhances reflective diffraction from a biograting formed on the substrate. Since Gustafson's substrate is specifically designed for their biograting immunoassay, and this assay is label free (i.e., it does not make use of fluorescently labeled probes), it is my judgment that a skilled worker in this field at the time that our invention was made would not have been led to our invention by Gustafson in combination with the other cited references. I do not believe that a person skilled in the art would have seen any advantage in combining the teachings of Gustafson and the other references to which the Examiner has referred, namely Pease, Wagner and Barrett, since Gustafson's teaching of the use of a flat substrate of silicon dioxide on reflective metal would have been viewed as specific to their particular label-free assay.

7. More specifically, with regard to the array substrate disclosed by Gustafson, the reference provides no teaching with regard to a suitable array substrate for a fluorescence-based assay, and certainly not for optimization of such an array substrate, as claimed. In experiments conducted by me or under my direction at Chiron, the fluorescent signal obtained from a labeled protein bound to an array having various thicknesses of silicon dioxide and otherwise constructed as claimed was tested. At oxide thicknesses below 200Å (e.g., thicknesses of about 110 to 140Å) no signal was detected. The signal obtained from arrays having silicon dioxide thicknesses in the 1200-1300Å range was poor. Intermediate silicon dioxide thicknesses, however, i.e., greater than 200Å and in particular about 800-900Å

resulted in dramatically stronger signal. Accordingly, we determined that amplification of the fluorescent signal used in assays conducted with arrays in accordance with the present invention is enhanced by using a silicon dioxide layer thickness of about 200-900 Å. These experiments demonstrate that our claimed array is not effective for its intended purpose across the whole range of silicon dioxide thicknesses (100-3000Å) disclosed by Gustafson and is optimized within the specific, critical claimed sub-range of 200-900Å of silicon dioxide thickness.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true. I further declare that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both (under Section 1001 of Title 18 of the United States Code), and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Deborah Charych

Deborah Charych

4/6/05

Date

(10) RELATED PROCEEDINGS APPENDIX

None.